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# X-Linked Mental Retardation With Neonatal Hypotonia in a French Family (MRX15): Gene Assignment to Xp11.22-Xp21.1

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**Linkage analysis was performed in a family with non-specific X-linked mental retardation (MRX 15). Hypotonia in infancy was the most remarkable physical manifestation. The severity of mental deficiency was variable among the patients, but all of them had poor or absent speech. Significant lod scores at a recombination fraction of zero were detected with the marker loci DXS1126, DXS255, and DXS573 (Zmax = 2.01) and recombination was observed with the two flanking loci DXS164 (Xp21.1) and DXS988 (Xp11.22), identifying a 17 cM interval. This result suggests a new gene localization in the proximal Xp region. In numerous families with non-specific X-linked mental retardation (MRX), the corresponding gene has been localized to the paracentromeric region in which a low recombination rate impairs the precision of mapping.**



**KEY WORDS: X-linked mental retardation, gene mapping, MRX, linkage analysis, proximal Xp, congenital hypotonia**

## INTRODUCTION

Progress towards identification of genes implicated in non-specific or in syndromal X-linked mental retardation (MRX and MRXS) is of great medical interest, as it is estimated that 1/600 males born has a form of X-linked mental retardation [Herbst, 1980; Opitz and Sutherland, 1984]. Fifty-seven syndromes and 25 non-specific MRX families have been listed thus far [Neri et al., 1994; Gendrot et al., 1994; Lazzarini et al., 1995; Martinez et al., 1995]. While syndromes are identifiable on the basis of a recognizable pattern of physical traits, making pooling of linkage information from different families possible, each MRX family must be studied separately. Linkage studies have been reported in 32 MRX families and at least 6 different MRX loci can be expected according to the non-overlapping localizations described [Lubs et al., 1996], but the real number of MRX genes is unknown.

Mental retardation can result from mutations in a great variety of genes, some of them expressed only in the brain and others involved in brain development or cellular adhesion or in various metabolic systems, making the candidate gene approach difficult.

We report here the brief clinical description and gene regional localization of one family with X-linked mental retardation (MRX15).

## MATERIALS AND METHODS

Five males in the family were affected over two generations, and the pedigree was consistent with an X-linked condition (Fig. 1). Clinical studies were performed at home by one of us (Cl.M.). The three living affected males, their parents, one healthy brother, and two healthy uncles were examined. Measurements and morphological findings were compared between patients and healthy relatives in order to identify what trait(s) was(were) related to the condition.

A neuro-psychologist (F.V.) tested the three affected males (III-1, III-4, and III-5; aged 31, 27, and 25 years, respectively). All subjects were given the Columbia Mental Maturity Scale [Burgemeister et al., 1965] for mental age estimation. Short-term memory, oral language, graphic skills, and laterality were evaluated by the Wechsler Memory Scale revisited [Wechsler, 1987], the Boston Diagnostic Aphasia Examination [Goodglass and Kaplan, 1982], the Reproduction Geometrical Figures Test of McCarthy Scales for Children Abilities [McCarthy, 1977], and the Laterality Test of Edinburgh [Olfield, 1971], respectively.

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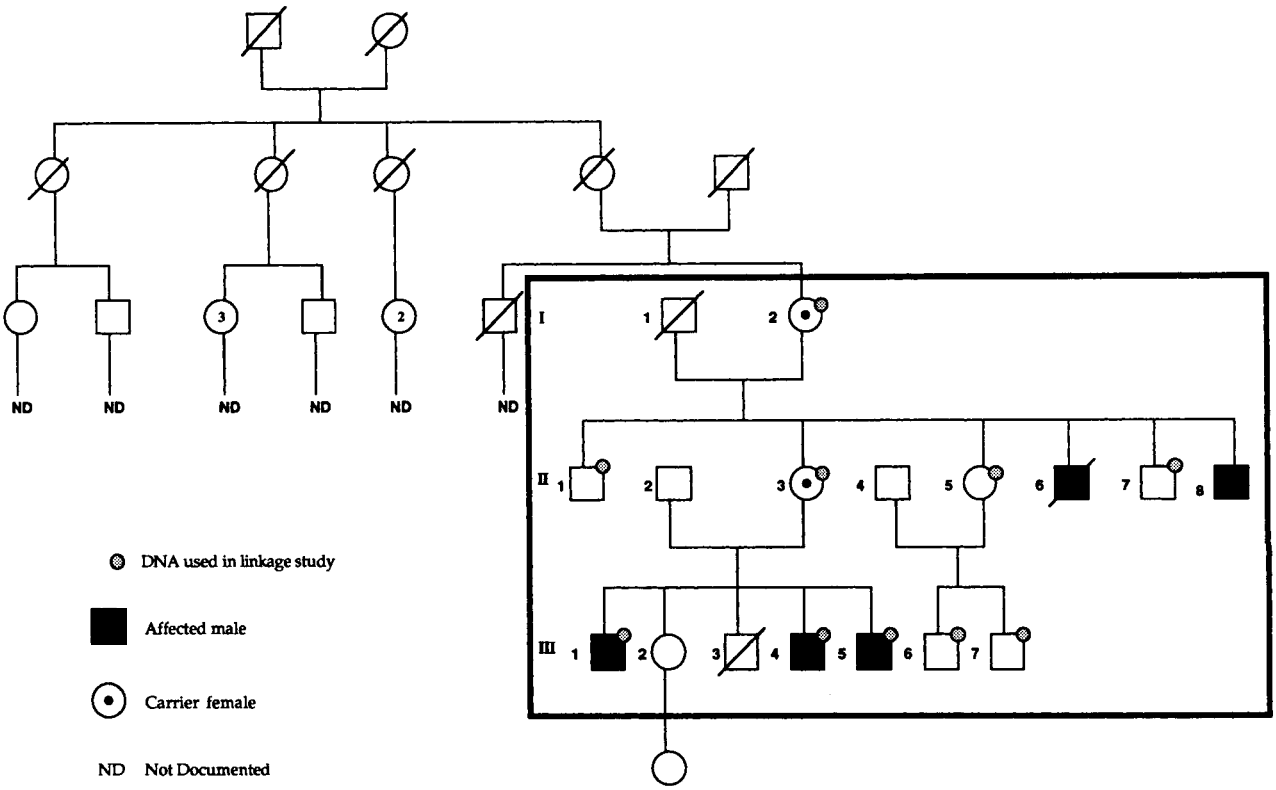


Fig. 1. Diagram of family pedigree.

Information was collected from physicians, social workers, and relatives on the history of affected males and on clinical characteristics of subjects who could not be examined.

Skeletal radiograms, specialized ophthalmological explorations and cerebral imaging were performed on affected patients.

III-4 was tested cytogenetically by standard and high resolution G and R banding and for fragile-X (FRAXA) by cytogenetic and molecular methods [probe StB12.3 on a EcoRI digest, Rousseau et al., 1991]. The FRAXE region [Knight et al., 1993] was tested in the same patient by PCR analysis. Hemoglobin H detection to identify the X-linked form of alpha thalassemia/mental retardation syndrome (ATRX) was performed. Results of these tests were normal.

Genomic DNA was extracted from venous blood. RFLP analysis was performed according to standard procedures, using either Southern blotting and conventional polymorphic DNA probes or PCR and digestion. PCR amplification of polymorphic CA-repeat sequences followed standard protocols, with 0.2 $\mu$Ci of alpha-($^{32}$P)dCTP in 15 $\mu$l of the PCR mixture. In total, 33 polymorphic DNA markers recognizing 33 loci spread over the X chromosome were analysed, including 19 CA repeat sequences (Table I).

Lod scores for linkage between the MRX gene and the polymorphic markers were calculated using the computer program MLINK for two-point analysis from the LINKAGE package [Lathrop et al., 1985]. The mutated allele frequency was set at 0.00006. Penetrance value was chosen at 1.0 for males and 0.0 for females. The mutation rate was set at 0.00. Allele frequencies were chosen at 0.5 and 0.33 for 2 and 3 alleles, respectively, for those markers for which these parameters were not precisely determined. The maximum expected lod score was calculated to be 2.01 for both the two and three allele system. Linkage analysis included three affected males, five healthy male relatives and two obligate carriers.

## RESULTS

### Clinical, Neuropsychological, and Imaging Results

The pedigree is shown in Figure 1 and photographs of affected and unaffected males in Figures 2 and 3.

Clinical data are summarized in Table II. The disease is characterized by congenital and subsequent hypotonia, considerable motor delay, severe mental deficiency with frequent hypoactivity, poor or absent speech, moderate slenderness, and scoliosis. No seizures, pyramidal symptoms, minor facial anomalies, deficiency, or excess of statural growth were reported. Testicular volume was normal. Unilateral divergent strabismus was observed in two affected males, associated with ptosis in one (III-5) and with slight facial asymmetry in the other (III-1). Another patient (III-4) had mild facial asymmetry without strabismus or patent facial nerve palsy. Facial asymmetry did not seem to be paternally inherited but was also observed in the unaffected

brother (III-3). Carrier females showed no physical abnormalities or mental retardation. The main neuropsychological impairments in affected males are summarized in Table III. Magnetic resonance imaging (MRI) showed cortical atrophy in III-1 (age 29 years). Brain scan was normal in III-5 (age 23 years).

### Linkage Results

Twenty-nine markers were fully or partly informative and 4 were not (DXS17, DXS1243, DXS84, and DXS426). Two-point lod scores for the 29 informative markers are presented on Table IV. No recombination occurred between the disease locus and 3 polymorphic loci (DXS1126, DXS255, and DXS573), for which a maximum lod score was obtained. DXS164 (Xp21.1) and DXS988 (Xp11.22) were the two flanking recombinant markers.

## DISCUSSION

In the family reported here, no physical manifestations distinguished between affected males and healthy relatives, and as such this condition can be considered a non-syndromic form of mental retardation (MRX15). Indeed, strabismus is often associated with several mental deficiencies and with cortical atrophy. Moderate scoliosis can be related to hypotonia. The facial asymmetry observed in some patients was also present in one unaffected male. Tallness and slimness with long thin hands and a long face were observed in affected males as in their healthy relatives.

The pattern of mental deficiency appeared initially to be variable in the family. One of the three affected

TABLE I. DNA Polymorphisms Used in the Linkage Study*

| Locus | Probe or PCR | Reference |
|---|---|---|
| DXS143 | dic56/BcII | Mandel et al., 1993 |
| DXS92 | pXG16/TaqI | Mandel et al., 1993 |
| DXS41 | p99.6/PstI | Mandel et al., 1993 |
| DXS1237 | (CA)n | Clemens et al., 1991 |
| DXS164 | pERT87.15/TaqI | Roberts et al., 1989 |
| DXS1242 | (CA)n | Feener et al., 1991 |
| DXS1110 | (CA)n | Roux et al., 1993 |
| OTC | O46/T46/DraI | Mandel et al., 1993 |
| DXS1068 | (CA)n | Gyappay et al., 1994 |
| DXS556 | (CA)n | Thiselton et al., 1993 |
| DXS7 | L1.28/TaqI | Mandel et al., 1993 |
| MAOA | (AC)18 CG (AC)3 | Black et al., 1991 |
| Syn/Araf | (CA)n | Kirchgessner et al., 1991 |
| TIMP | PCR/BgIII | Aldred and Wright, 1991 |
| PFC | (CA)n | Coleman et al., 1991 |
| **DXS1126** | **(CA)n** | Donelly et al., 1994 |
| **DXS255** | **M27β/PstI** | Mandel et al., 1993 |
| **DXS573** | **(CA)n** | Roustan et al., 1993 |
| DXS1000 | (CA)n | Généthon, unpublished |
| DXS988 | (CA)n | Gyapay et al., 1994 |
| ALAS2 | (CA)n | Cox et al., 1992 |
| AR1 | (CA)n | Donnelly et al., 1994 |
| DXS441 | (CA)n | Ram et al., 1991 |
| DXS3 | (CA)n | Stanier et al., 1991 |
| DXS94 | pXG12/PstI | Mandel et al., 1993 |
| DXS10 | 6A1/TaqI | Mandel et al., 1993 |
| DXS144.E | C11/TaqI | Mandel et al., 1993 |
| DXS52 | St14/TaqI | Mandel et al., 1993 |
| F8 | (CA)n/intr.13 | Lalloz et al., 1991 |

*The boldfaced type markers are those for which a Zmax > 2/theta = 0 was obtained.

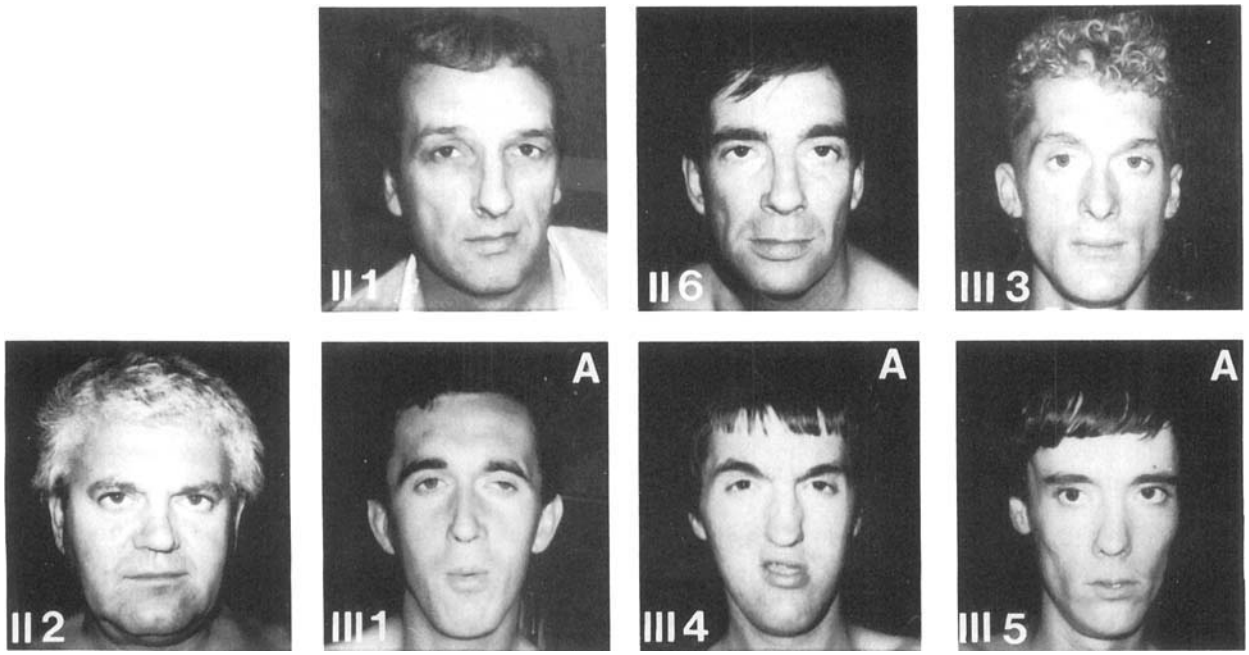


Fig. 2. Facial appearance of affected males and some of their healthy relatives. Subjects are identified by their number in family pedigree (Fig. 1). A: affected males.


Fig. 3. Facial appearance of affected males and some of their healthy relatives. Subjects are identified by their number in family pedigree (Fig. 1). A: affected males.

males (III-4) could not speak, used only non-verbal communication, and was completely dependent, while his brother (III-1) could talk, ride a bicycle, and had some social life. However, precise neuropsychological analysis showed that the 3 brothers were affected in the same developmental areas and that the difference in severity explained the difference in behaviour which was observed between them (Table III).

Neonatal hypotonia and intermittent hypoactivity in children and adults are the main manifestations besides mental retardation in this family. We have observed hypotonia in the neonatal period and infancy in several other MRX families (unpublished observations) and it has also been described in MRX12 in association with short stature and hypotelorism [Kerr et al., 1992], and in the XLMR with aphasia described by Wilson et al. [1992]. Hypotonia was also reported in association with other symptoms in several MRXS disorders (Table V) and the mapping region overlaps our localization in some of them. Thus, the same gene might be involved in an MRXS family as in our family and different mutations would explain the different clinical patterns.

Although only a certain part of the kindred seems to have mental retardation (Fig. 1) there is no additional argument for a fresh mutation in I-2 and her father was young (33 years old) when she was born.

The gene involved in MRX15 is mapped to the region Xp11.22-Xp21.1, flanked by DXS988 and DXS164, respectively. The interval is estimated to be 17 cM. Close linkage was found between the disease locus and the polymorphic DNA segments DXS255, DXS1126 and DXS573 which are localized at Xp11.23. These markers were also the only wholly informative markers in this region. The localization area could possibly be reduced by identifying additional microsatellite markers for which the carrier female I-2 would be informative.

The proximal Xp region might be rich in "mental retardation genes," as suggested by the 16 of 22 localized non-specific XMLR families which have been mapped to this region. These are MRX 1, 4, 5, 7–13, 17, 18, 21, and the family described by Wilson, all referenced in Neri [Neri et al., 1994], MRX14 [Gendrot et al., 1994] and MRX20 [Lazzarini et al., 1995]. However, as suggested above, it cannot be excluded that only a few genes could be responsible for the mental retardation in most of these families. In addition, the relatively low recombination rate in the pericentromeric region impairs the precision of mapping in these linkage studies.

The interval one can expect to map the gene in a large MRX family using the available highly informative markers along the X chromosome [Kerr et al., 1992; Hu et al., 1994] is not often shorter than 10–15 cM. As positional cloning is difficult if the localization area is over 2 or 3 megabases, several additional approaches have to be considered once an MRX gene has been mapped with linkage methods. Owing to non-specificity of clinical manifestations, it cannot be asserted that the same gene is mutated in two different MRX families, and the pooling of linkage results in order to refine the gene localization is inappropriate. More accurate studies of the natural history of the MRX entity combined with the use of neuropsychological tests might uncover some distinguishing parameters such as neonatal hypotonia, which is observed only in some MRX families. Comparative physical descriptions between affected males and their healthy relatives will highlight those physical traits associated with a potential phenotype. Identical neuropsychologi-

TABLE II. Clinical Findings in Affected (A) and Normal (N) Males*

| | II1 (N) | II2 (N) | II7 (N) | III3 (N) | III1 (A) | III4 (A) | III5 (A) |
|---|---|---|---|---|---|---|---|
| Age at examination (yr) | 45 | 51 | 38 | 22 | 25 | 21 | 19 |
| Physical measurements | | | | | | | |
| Height (cm) | 185 | 176 | 179 | 182 | 182 | 188 | 177 |
| Weight (kg) | 83 | 85 | 63 | 65 | 71 | ND[b] | Thin |
| OFC (cm) | 61 | 57 | 57 | 55.5 | 57 | 57.5 | 57 |
| Hand length (cm) | 21 | 20 | 21 | 19 | 20 | 18 | 18 |
| Minor anomalies | No | No | No | Facial asymmetry | Slight facial asymmetry | Slight facial asymmetry | N |
| Dermatoglyphics | NR[a] | NR | Bilateral distally reported axial triradius, whorls on 9/10 fingerprints | NR | NR | NR | Bilateral distally reported axial triradius |
| Developmental history | NR | NR | NR | | | | Prematurity |
| Neonatal hypotonia (y/n) | | | | No | Yes | Yes | Yes |
| Walking (months) | | | | 14 | 25 | 27 | 36 |
| Urine continence (yr) | | | | N | 10 | 20 | 12 |
| Day | | | | 13 | 13 | No | No |
| Night | | | | | | | |
| Seizures | No | No | No | No | No | No | No |
| Neurological signs | | | | | | | |
| Reflexes | N | N | N | N | N | N | N |
| Muscle mass and tone | N | N | N | N | N | N | N |
| Spinal curvature | No | No | No | No | Moderate scoliosis | Moderate scoliosis | Scoliosis |
| Vision | Astigmatism | Myopia | Myopia | Myopia (L > R) | Strabismus | N | Strabismus |
| Hearing | N | N | N | N | N | N | N |

* Neuropsychological data are summarized in Table III.
[a] NR = not remarkable.
[b] ND = not documented.

TABLE III. Main Neuropsychological and Behavioural Patterns in the Three Living Affected Males*

| | | | Short-term memory | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Digit span | | Visuo-spatial span | | Oral language | | | | | |
| | Laterality | Mental age and severity | Forward | Backward | Forward | Backward | Comprehension | Speech | Motor abilities | Graphic skills | Autonomy and social life | General behaviour |
| III-4 (27 yr) | R | <24 months, profound | 0 | 0 | 0 | 0 | Very limited | Usually non-verbal communication<br>Repeated monosyllabic words | Walking | Limited to circle | No autonomy (lives in a special center)<br>Good social behaviour | Hyperactivity and hyperkinetic syndrome<br>Verbal and gestural perseverations<br>Distractibility<br>Extrovert and cooperative nature |
| III-5 (25 yr) | L | 2.3 years, profound | 1 | 0 | 1 | 0 | Limited to simple orders | Limited to single words<br>No sentences<br>Bad words articulation | Walking | Doodling | No autonomy (lives in a special center)<br>Good social behaviour | Apathy, apragmatism and slowness in carrying on tasks<br>Anxiousness. Shyness<br>Verbal perseverations<br>Distractibility<br>Stubbornness |
| III-1 (31 yr) | R | 4.3 years, severe | 1 | 0 | 2 | 0 | Normal | Accurate sentences<br>Bad words articulation<br>Poor lexical stock<br>Echolaly and logorrhea | Walking<br>Cycling | Limited to simple geometrical figures | Partial autonomy (works in a training center)<br>"sheltered workshop"<br>Good social behaviour | Hyperactivity and twitchiness<br>Anxiousness and logorrhea<br>Joviality and cooperative nature<br>Verbal and gestural perseverations<br>Distractibility<br>Impulsiveness |

* The order of individuals has been selected according to their degree of severity.

TABLE IV. Two-Point Lod Scores Between the Gene and Chromosome Markers*

| Localization | Locus | Probe or PCR | Lod score for theta | | | | | | | | Z max | Theta-max | Number of informative meioses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.00 | 0.001 | 0.01 | 0.05 | 0.10 | 0.20 | 0.30 | 0.40 | | | |
| Xp22.32 | DXS143 | dic56/BclI | 0.81 | 0.80 | 0.79 | 0.72 | 0.62 | 0.42 | 0.22 | 0.05 | 0.81 | 0.00 | 6 |
| Xp22.1 | DXS92 | pXG16/TaqI | −∞ | −1.89 | −0.90 | −0.24 | 0.01 | 0.18 | 0.20 | 0.14 | 0.20 | 0.30 | 6 |
| Xp22.1 | DXS41 | p99.6/PstI | −∞ | −1.89 | −0.90 | −0.24 | 0.01 | 0.18 | 0.20 | 0.14 | 0.20 | 0.30 | 6 |
| Xp21.1 | DXS1237 | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp21.1 | DXS164 | pERT87.15/TaqI | −∞ | −0.87 | 0.10 | 0.66 | 0.78 | 0.69 | 0.46 | 0.20 | 0.78 | 0.10 | 10 |
| Xp21.1 | DXS1242 | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp21.1 | DXS1110 | (CA)n | 0.20 | 0.20 | 0.20 | 0.20 | 0.18 | 0.13 | 0.07 | 0.02 | 0.20 | 0.00 | 4 |
| Xp11.4 | OTC | O46/T46/DraI | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.4 | DXS1068 | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.4 | DXS556 | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.4-p11.3 | DXS7 | L1.28/TaqI | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.3 | MAOA | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.3 | Syn/Araf | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.3 | TIMP | PCR/BgIII | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.3 | PFC | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| **Xp11.23** | **DXS1126** | **(CA)n** | 2.01 | 2.01 | 1.98 | 1.84 | 1.66 | 1.26 | 0.84 | 0.39 | 2.01 | 0.00 | 8 |
| **Xp11.23** | **DXS255** | **M27β/PstI** | 2.01 | 2.01 | 1.98 | 1.83 | 1.65 | 1.25 | 0.83 | 0.39 | 2.01 | 0.00 | 10 |
| **Xp11.23** | **DXS573** | **(CA)n** | 2.01 | 2.01 | 1.98 | 1.83 | 1.65 | 1.25 | 0.83 | 0.39 | 2.01 | 0.00 | 10 |
| Xp11.22 | DXS1000 | (CA)n | 1.11 | 1.11 | 1.09 | 1.04 | 0.96 | 0.78 | 0.57 | 0.31 | 1.11 | 0.00 | 6 |
| Xp11.22 | DXS988 | (CA)n | −∞ | −1.29 | −0.32 | 0.26 | 0.4 | 0.39 | 0.25 | 0.09 | 0.40 | 0.10 | 10 |
| Xp11.21 | ALAS2 | (CA)n | −∞ | −2.40 | −1.40 | −0.72 | −0.44 | −0.19 | −0.08 | −0.02 | 0.00 | 0.50 | 4 |
| Xq12 | AR | (CA)n | −∞ | −0.93 | −0.02 | 0.55 | 0.70 | 0.67 | 0.50 | 0.28 | 0.70 | 0.10 | 10 |
| Xq13.2-q13.3 | DXS441 | (CA)n | −∞ | −2.40 | −1.40 | −0.72 | −0.44 | −0.19 | −0.08 | −0.02 | 0.00 | 0.50 | 4 |
| Xq21.33 | DXS3 | (CA)n | −∞ | −1.59 | −0.59 | 0.10 | 0.37 | 0.52 | 0.46 | 0.29 | 0.52 | 0.20 | 8 |
| Xq22.2 | DXS94 | pXG12/PstI | −∞ | −3.98 | −2.00 | −0.73 | −0.28 | 0.00 | 0.03 | 0.01 | 0.03 | 0.30 | 10 |
| Xq26.1 | DXS10 | 6A1/TaqI | −∞ | −7.89 | −4.89 | −2.80 | −1.90 | −1.02 | −0.53 | −0.22 | 0.00 | 0.50 | 6 |
| Xq26.2 | DXS144.E | C11/TaqI | −∞ | −4.29 | −2.32 | −1.02 | −0.54 | −0.17 | −0.04 | 0.00 | 0.00 | 0.40 | 10 |
| Xq28 | DXS52 | St14/TaqI | −∞ | −4.59 | −2.58 | −1.17 | −0.59 | −0.09 | 0.10 | 0.11 | 0.11 | 0.40 | 8 |
| Xq28 | F8 | (CA)n/intr.13 | −∞ | −6.52 | −3.54 | −1.54 | −0.77 | −0.14 | 0.08 | 0.11 | 0.11 | 0.40 | 10 |

* Maximum lod scores were obtained for the three bold-typed markers. MRX15 localization between the two recombinant markers is indicated by two lines.

TABLE V. MRXS With Hypotonia*

| Syndrome: original report/gene localization | Associated symptoms | Gene mapping |
|---|---|---|
| Allan-Herndon-Dudley: Allan et al., 1944/Schwartz et al., 1990 | Muscular atrophy, spasticity | Xq13-q21.3 |
| Coffin-Lowry: Coffin et al., 1966/Biancalana et al., 1992 | Coarse face, drumstick phalanges, skeletal anomalies | Xp22.2-p22.1 |
| Fragile X (FRAXA): Martin and Bell, 1943/Oberlé et al., 1991 | Macrocephaly, long face, long ears, macroorchidism | Xq27.3 |
| FG syndrome: Opitz and Kaveggia, 1974 | Macrocephaly, agenesis of corpus callosum, Gastro-intestinal anomalies, deafness | |
| Lujan-Fryns: Lujan et al., 1984 | Marfanoid habitus, triangular face, narrow palate, hypernasal voice | |
| MRXS 5: Pettigrew et al., 1991 | Long coarse face, hydrocephaly, spasticity, ataxia, seizures | Xq26-q27.1 |
| Porteus: Porteus et al., 1992 | Microcephaly, small testes, facial dysmorphism, digital flexion | Xp11.4-q13 |
| Smith-Fineman-Myers: Smith et al., 1980 | Microcephaly, short stature, spaced teeth, short philtrum, Prominent lower lip, seizures | |
| Snyder-Robinson: Snyder and Robinson, 1969/Arena et al., 1992 | Wide-base gait, asthenic body build, disequilibrium, Long thin face, high narrow palate | Xp22.3-p21.3 |
| Zollino: Zollino et al., 1992 | Peculiar face, dysgenesis of corpus callosum, Failure to thrive, seizures | |

* Modified from Neri et al., 1994.

cal pattern or natural history in the different families considered might legitimate pooling of the linkage results, but studies are only beginning in this field. Nevertheless, intrafamily phenotype variability and/or allelism between some MRX and MRXS may interfere with these phenotyping efforts.

The systematic search for mutations in a candidate gene in affected patients of MRX families is another solution for gene localization after linkage studies. Cloned genes from cytogenetic anomalies are among possible candidates. A number of balanced X-autosome translocations associated with mental retardation have been described with a breakpoint in the Xp11 region [Teboul et al., 1989] and it has been assumed that a disrupted gene on the X chromosome could explain mental deficiency in several of them. Cloning the X breakpoints to identify the corresponding gene(s) is in progress in some patients [Ropers et al., 1994] with a view to test them as candidate(s) in MRX families. Isolation of XLMR genes implicated in contiguous gene syndromes [Ballabio and Andria, 1992; Bach et al., 1992] may also provide candidate genes but cytogenetic or molecular deletions appear to be infrequent in proximal Xp.

Some MRXS reported by Aarskog, Miles (MRXS4), Prieto (MRXS2), Renpenning, Sutherland (MRXS3), Wilson (MRXS6), and Porteus [Neri et al., 1994] are localized between Xp11.22 and Xp21.1. Although the corresponding clinical patterns are different from that described here, some MRX and MRXS might be allelic disorders. Such a situation is illustrated by mutations in the cell adhesion molecule L1, which have been recently reported in four clinically different syndromes [Willems et al., 1995], i.e., X-linked hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS), MASA syndrome, X-linked complicated spastic paraparesis (SP1), and X-linked corpus callosum agenesis (ACC). A few genes in Xp proximal region which are involved in brain function have been cloned, e.g., SYP [Özçelik et al., 1990] and SYN 1 [Südhof, 1990]. Moreover, a mutation in the monoamine oxidase A gene was identified in a family with borderline mental retardation and abnormal behaviour [Brunner et al., 1993]. Finally, the promoter region of one of the brain dystrophin transcripts is included in the mapping region in the family reported here. These different genes are candidate genes for MRX. On the other hand, systematic mapping of brain cDNAs [Polymeropoulos et al., 1993] will probably assign many X-linked genes which are either expressed only in the brain or pleiotropic and they will be also candidates for XLMR.

Thus, it appears likely that while clinical or biological particularities, distinctive behaviour, specific neuropsychological pattern, or particular developmental history may point to the gene function in some MRX families and help to select one particular gene among the cloned genes mapped to the region, many candidate genes with compatible localization will have to be systematically tested for mutations in affected patients in other families. Whatever the approach, collaborative studies will be necessary to achieve cloning of the MRX genes.

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